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Structure–Activity Relationships of Herbicidal Aryltriazolinones*

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Abstract: A series of substituted aryltriazolinones, known to inhibit protoporphyrinogen oxidase, were prepared and their structure–activity requirements at positions 4 and 5 of the aromatic ring investigated. A QSAR equation obtained for substituents at the 5 position identified the hydrophobicity term π and the Sterimol minimum width B_1 as the two parameters affecting *in-vitro* biological activity. Greenhouse pre-emergence activity correlated with *in-vitro* activity and the hydrophobicity term π of the substituent at that position. It was found that the phenoxy-4-oxyacetate group at aromatic position 5 was an outlier and had to be considered separately. SAR analysis of substituents at aromatic position 4 revealed that two different models were required to explain all observed substituent effects. In the first model, where the 5 position was occupied by hydrogen, the 4-chlorobenzyloxy group at aromatic position 4 gave the best compound. The second model, where the 5 position of the aromatic ring was occupied by a group other than hydrogen, resulted in a QSAR equation, previously derived, which links substituent effects at position 4 with π and with the electronic para inductive term F_p. In this model the chloro group provides optimum biological activity. The need to separate the aryltriazolinone herbicides into several different classes in order to explain their substituent effects at aromatic positions 4 and 5 could be rationalized if more than one binding conformation, within the same binding site, is possible.

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1 INTRODUCTION

Herbicides that act by inhibiting protoporphyrinogen oxidase (PPO) have been known for several decades. Acifluorfen, oxyfluorfen and oxadiazon are among several commercial PPO-inhibiting herbicides that have been in use for many years, though their mechanism of action had not been elucidated till fairly recently.[1,2] Our investigations of PPO inhibitors have resulted in the discovery of several highly active aryltriazolinone herbicides such as compounds **1**, **20** and **21**; sulfentrazone,[3] a pre-emergence soybean herbicide; and carfentrazone-ethyl,[4] a post-emergence cereal herbicide (Fig. 1). The chemical groups at positions 4 and 5 of the aromatic ring of these molecules represent a broad range of physicochemical properties, from the highly lipophilic ($\pi = 2{\cdot}40$), electron-donating ($\sigma_p = -0{\cdot}23$) 4-chlorobenzyloxy group in compound **21** to the considerably less lipophilic ($\pi = 0{\cdot}71$), electron-withdrawing ($\sigma_p = 0{\cdot}23$) chloro group in compound **1**. In the case of aromatic position 5, all three chemical groups—the hydrophilic methanesulfonylamino group ($\pi = -1{\cdot}18$) of sulfentrazone, the relatively neutral propargyloxy group ($\pi = 0{\cdot}02$) of compound **1**, and the lipophilic phenoxy-oxyacetate group ($\pi = 2{\cdot}30$) of compound **20**—resulted in highly active molecules.

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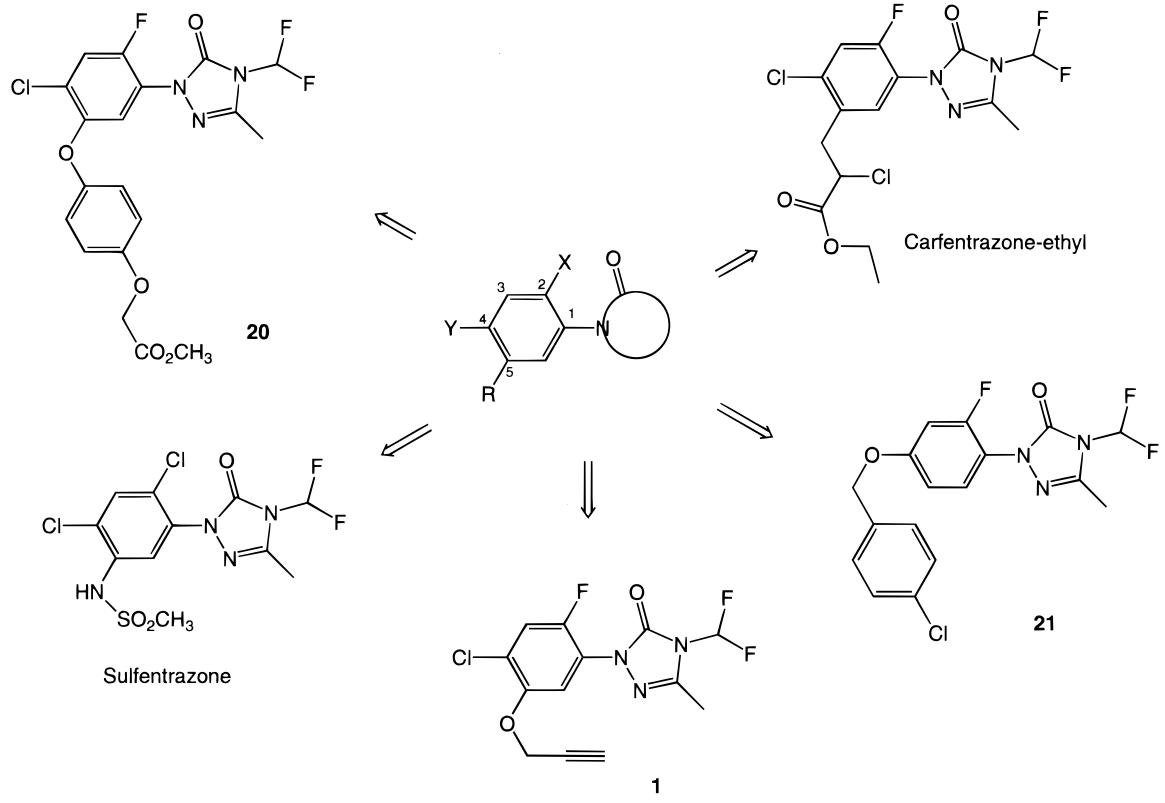


Fig. 1. 2-Halo-4,5-disubstituted phenyl triazolinones.

This diversity of chemical groups at the 4 and 5 aromatic positions of aryltriazolinones prompted us to investigate further the structure–activity of these molecules.

All the compounds studied were derivatives of 4-difluoromethyl-4,5-dihydro-3-methyl-1*H*-1,2,4-triazol-5-one, and, in the following discussion, the term 'triazolinone' refers to this nucleus substituted in the 1 position by the group indicated.

2 MATERIALS AND METHODS

2.1 Synthesis of test compounds

All compounds discussed in Tables 1, 4 and 6 were synthesized by methods previously published.[3,5,6] The structural assignments of these compounds were based on their IR, mass and [^{1}H]NMR spectra. Compounds **21–25**, Table 5, were prepared from the corresponding (2-fluorophenyl-4-hydroxyphenyl)triazolinone.[6] Melting points were taken in open capillaries and are uncorrected.

2.1.1 [4-(4-Chlorobenzyloxy)-2-fluorophenyl]triazolinone (21)

A mixture of (2-fluoro-4-hydroxyphenyl)triazolinone (**33**)[6] (0·75 g, 2·9 mmol), potassium carbonate (0·61 g, 4·4 mmol) and *p*-chlorobenzyl chloride (0·71 g, 4·4 mmol) in dimethylformamide (60 ml) was stirred at 70°C for 18 h. The solution was allowed to cool to room temperature, poured into water (200 ml), and the precipitate that formed collected by filtration, washed with water, and dried to give 1·04 g of crude **21** in 98% yield; m.p. 121–122°C. [^{1}H]NMR (deuterochloroform) δ: 2·45 (s, 3H), 5·05 (s, 2H). 6·79–7·4 (m, 8H) ppm.

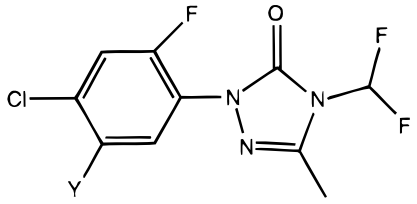
2.1.2 (2-Fluoro-4-hydroxy-5-nitrophenyl)triazolinone intermediate

33 (2·0 g, 7·7 mmol) was dissolved in concentrated sulfuric acid (40 ml) and the solution cooled to 0°C. Nitric acid (70% concentration, 0·5 ml, 7·7 mmol) was added dropwise while maintaining the reaction temperature below 5°C. The solution was allowed to stir at 25°C for 3 h. The solution was poured over ice and the oily precipitate was extracted with ether, the organic layer dried with magnesium sulfate, and the solvent removed under vacuum. The residue was chromatographed (silica gel, methylene chloride + ethyl acetate; 95 + 5 by volume). Yield 1·96 g, 84%; m.p. 93–95°C. [^{1}H]NMR (deuterochloroform) δ: 2·45 (s, 3H), 6·82–7·23 (m, 2H), 8·34 (d, 1H, J_{HF} = 9·0 Hz), 10·82 (s, 1H) ppm.

2.1.3 [4-(4-Chlorobenzyloxy)-2-fluoro-5-nitrophenyl]-triazolinone (22)

A mixture of (2-fluoro-4-hydroxy-5-nitrophenyl)triazolinone (1·0 g, 3·3 mmol), potassium carbonate (0·69 g, 5·0 mmol) and *p*-chlorobenzyl chloride (0·8 g, 5·0 mmol) in dimethylformamide (60 ml) was stirred at 70°C for 18 h. The solution was allowed to cool to room temperature, and then poured into water (200 ml).

TABLE 1
Biological Activities and Physicochemical Parameters for 4-Chloro-2-fluoro-5-substituted Phenyl Triazolinones



Compound	*Y*	pI_{50}	π	B_1	σ	L	ED_{90} (*kg ha*$^{-1}$)
1	$OCH_2C{\equiv}CH$	7·6	0·02	1·35	0·12	6·58	0·03
2	$OCH_2CH{=}CH_2$	7·5	0·62	1·35	0·09	6·30	0·125
3	OCH_3	7·5	−0·02	1·35	0·12	3·98	0·125
4	OH	7·2	−0·67	1·35	0·12	2·74	0·30
5	CH_2OCH_3	7·1	−0·78	1·52	0·08	4·91	0·50
6	$NHSO_2Et$	7·1	−0·64	1·35	0·20	6·07	0·062
7	$OCOCH_3$	7·1	−0·64	1·35	0·39	4·87	0·30
8	CH_3	7·0	0·56	1·52	−0·07	3·00	0·50
9	H	6·8	0	1·00	0	2·06	0·50
10	$NHSO_2CH_3$	6·7	−1·18	1·50	0·20	4·06	0·03
11	OC_6H_5	6·6	2·08	1·35	0·25	4·51	1·0
12	Cl	6·5	0·71	1·80	0·37	3·52	1·0
13	Br	6·5	0·86	1·95	0·39	3·83	1·0
14	C_6H_5	6·3	1·96	1·70	0·06	6·28	2·0
	High	7·6	2·08	1·95	0·39	6·58	2·0
	Low	6·3	−1·18	1·00	−0·07	2·06	0·03

The precipitate was collected by filtration, washed with water, and dried to give 1·20 g of crude compound **22** in 85% yield; m.p. 201–202°C. [^{1}H]NMR (deuterochloroform) δ: 2·45 (s, 3H), 5·05 (s, 2H). 6·82–7·42 (m, 6H), 8·18 (d, 1H, J_{HF} = 9·0 Hz) ppm.

*2.1.4 [2-Fluoro-4-(4-chlorobenzyloxy)-5-aminophenyl]-triazolinone (**23**)*

A solution of **22** (0·60 g, 1·4 mmol), acetic acid (50 ml) and water (10 ml) was heated to 50°C and kept at this temperature while iron dust (0·60 g, 1·07 mmol) was added. The solution was stirred at 25°C for 1 h, poured into water and filtered through a Celite® pad. The solution was extracted with ethyl acetate, the organic layer dried with magnesium sulfate, and the solvent removed under vacuum. The residue was chromatographed (silica gel, methylene chloride + ethyl acetate; 90 + 10 by volume). Yield 0·46 g, 87%; m.p. 165–166°C. [^{1}H]NMR (deuterochloroform) δ: 2·45 (s, 3H), 3·78 (s, 2H), 5·10 (s, 2H), 6·65–7·4 (m, 7H), 8·34 (d, 1H, J_{HF} = 9·0 Hz), 10·82 (s, 1H) ppm.

*2.1.5 [2-Fluoro-4-(4-chlorobenzyloxy)-5-methane-sulfonylaminophenyl]triazolinone (**24**)*

A solution of **23** (1·0 g, 2·5 mmol), methanesulfonyl chloride (0·28 g, 2·5 mmol) and pyridine (0·20 g, 2·5 mmol) in methylene chloride (20 ml) was stirred at 25°C for 18 h. The solution was washed with water, dried with magnesium sulfate and chromatographed (silica gel, methylene chloride + ethyl acetate, 95 + 5 by volume). Yield 1·05 g, 88%; m.p. 182–185°C. [^{1}H]NMR (deuterochloroform) δ: 2·45 (s, 3H), 2·98 (s, 3H), 5·05 (s, 2H), 6·65–7·65 (m, 8H) ppm.

2.1.6 5-Chloro-2-fluoro-4-hydroxyphenyl triazolinone intermediate

A solution of 2-fluoro-4-hydroxyphenyl triazolinone **33** (1·25 g, 4·8 mmol) and sulfuryl chloride (0·65 g, 4·8 mmol) in methylene chloride (30 ml) was stirred at 25°C for 18 h. The solution was washed with water, dried with magnesium sulfate and chromatographed (silica gel, methylene chloride + ethyl acetate, 95 + 5 by volume). Yield 1·25 g, 89%; m.p. 130–132°C. [^{1}H]NMR (deuterochloroform) δ: 2·45 (s, 3H), 6·23 (s, 1H), 6·83–7·43 (m, 3H) ppm.

*2.1.7 [5-Chloro-2-fluoro-4-(4-chlorobenzyloxy)phenyl]-triazolinone (**25**)*

A mixture of (5-chloro-2-fluoro-4-hydroxyphenyl)triazolinone (0·75 g, 2·6 mmol), potassium carbonate (0·54 g, 3·9 mmol) and *p*-chlorobenzyl chloride (0·63 g, 3·9 mmol) in dimethylformamide (60 ml) was stirred at 70°C for 18 h. The solution was allowed to cool to room temperature, then poured into water (200 ml). The precipitate was collected by filtration, washed with water and dried to give 1·03 g of crude **25** in 95% yield;

TABLE 2
Correlation Matrix

	π	σ	B_1	L
π	1·00			
σ	0·01	1·00		
B_1	0·28	0·46	1·00	
L	0·14	0·06	0·15	1·00

m.p. 177–178°C. [^{1}H]NMR (deuterochloroform) δ: 2·45 (s, 3H), 5·12 (s, 2H). 6·79–7·52 (m, 7H) ppm.

2.2 Biological activity

2.2.1 Hydroponic cucumber assay

This assay was adapted from a published procedure.[7] Two 55-mm explants from five-day-old etiolated cucumbers (*Cucumis sativus* L. cv. Wisconsin), retaining the cotyledons, apical meristem and upper portions of the stem, were placed into vials containing 20 ml of B5 medium without sucrose, hormones or vitamins.[8] The explants had been treated with replicated three-fold serial dilutions of chemicals at five rates, ranging from 10^{-5} to $10^{-7.5}$ M, and were incubated under continuous light at 100 μE m^{-2} s^{-1} at 25°C for 10 days. A pI_{50} value (− log concentration in mol litre^{-1}) for each test chemical was calculated from the relative growth inhibition measured as the weight gain after treatment relative to that of untreated controls.

2.2.2 Pre-emergence herbicidal evaluation

The seeds of ivyleaf morningglory (*Ipomoea hederacea* (L.) Jacq.) were planted in furrows in steam-sterilized sandy loam soil contained in disposable fiber flats. A topping soil was placed uniformly on top of each flat to a depth of approximately 0·5 cm. A stock solution of the candidate herbicide was prepared by dissolving a predetermined weight of the compound in 20 ml of water + acetone (50 + 50 by volume) containing 5 g litre^{-1} Tween® 20 surfactant. Thus, for an application rate of 3·0 kg ha^{-1} of herbicide, 0·21 g of the candidate herbicide was dissolved in 20 ml of the aqueous acetone to prepare the stock solution. For the 300 g ha^{-1} rate of application, a 1·0 ml portion of stock solution was diluted with water + acetone (50 + 50 by volume) to 35 ml, the volume required for a spray volume of 1000 litre ha^{-1}. The flats were watered, then sprayed with the appropriate amount of a solution of the test compound. The concentration of the test compound in solution was varied to give a range of application rates, generally 3·0 kg ha^{-1} and submultiples thereof. The flats were placed in the greenhouse, watered regularly at the soil surface for 14 days, and phytotoxicity data recorded. Herbicidal activity was assessed visually on a 0–100% scale (0% no effect; 100% complete kill). Biological activity in Tables 1 and 5 is presented as the pre-emergence application rate required to give 90% control (ED_{90}) as compared with untreated plants.

2.3 Substituent parameters and QSAR method

The biological activities and physicochemical parameters for the 4-chloro-2-fluoro-5-substituted phenyl triazolinones are summarized in Table 1.

The compounds selected represent a broad range of values for the hydrophobicity term π, the electronic term σ, the Sterimol terms B_1 and L and were confirmed as a representative set by using correlation analysis (Table 2). Statistical analysis was performed with BMDP[9] software on a VAX 8530 computer.

TABLE 3
Biological Activities and Physical Properties of 4-Chloro-2-fluoro-5-substituted Phenyl Triazolinones

			pI_{50} (−log M)	
Compound	*m.p. (°C)*	*Substituent*	*Predicted*	*Observed*
1	80–81	$OCH_2C{\equiv}CH$	7·3	7·6
2	53–55	$OCH_2CH{=}CH_2$	7·2	7·5
3	86–88	OCH_3	7·3	7·5
4	147–152	OH	7·2	7·2
5	oil	CH_2OCH_3	7·1	7·1
6	162–163	$NHSO_2Et$	7·1	7·1
7	oil	$OCOCH_3$	7·2	7·1
8	119–120	CH_3	7·1	7·0
9	88–91	H	6·9	6·8
10	156–159	$NHSO_2CH_3$	6·9	6·7
11	oil	OC_6H_5	6·5	6·6
12	111–113	Cl	6·7	6·5
13	93–95	Br	6·2	6·5
14	oil	C_6H_5	6·3	6·3

3 RESULTS

3.1 Substituent effect at aromatic position 5 of aryltriazolinones

The set of 14 compounds was subjected to a multiple linear regression analysis using the cucumber inhibition data pI_{50} values from Table 1. The quantitative structure–activity relationship model in eqn (1) describes the relationship between structure and inhibition of hydroponic cucumber. In this equation n is the number of compounds, s is standard error of the model, and r^2 the explained variance. The values in parentheses are the standard error for the coefficients. The Sterimol term B_1, the squared term of B_1 and π correlated with the observed biological activity. These three terms accounted for 78% of the biological activity. These results would imply that the minimum radius B_1 and the hydrophobicity term π follow a parabolic relationship with biological activity. Biological activity reaches an optimum when $B_1 = 1{\cdot}35$ and $\pi = 0{\cdot}02$, then decreases beyond these values.

$$pI_{50} = 7{\cdot}02(\pm 2{\cdot}351)B_1 - 0{\cdot}18(\pm 0{\cdot}045)\pi^2 - 2{\cdot}57(\pm 0{\cdot}775)B_1^2 + 2{\cdot}51 \quad (1)$$
$$n = 14 \quad r^2 = 0{\cdot}78 \quad s = 0{\cdot}216$$

A stepwise regression analysis for the development of eqn (1) shows that the square of the Hansch hydrophobicity term π accounted for 38% of the variance of biological activity. Addition of the Sterimol term B_1 and its squared term improved the explained biological variance to 78%.

By use of eqn (1), pI_{50} values were calculated and compared with measured values as shown in Table 3. The predicted potency of all the compounds was within one standard deviation of the observed values.

Equation (2) shows that there was some correlation between the hydroponic assay and greenhouse activity, with the pI_{50} term alone explaining 45% of the biological variance. In eqn (3), addition of the π term significantly improved the regression equation, with 60% of biological variance explained by the pI_{50} values and the hydrophobicity term π.

$$\log 1/ED_{90} = 0{\cdot}95(\pm 0{\cdot}30)pI_{50} - 9{\cdot}08 \quad (2)$$
$$n = 14 \quad r^2 = 0{\cdot}45 \quad s = 0{\cdot}447$$

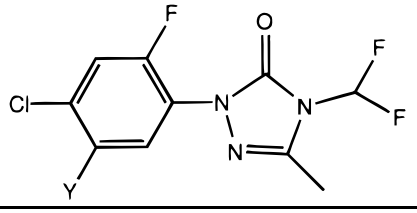
$$\log 1/ED_{90} = 0{\cdot}66(\pm 0{\cdot}30)pI_{50} + 0{\cdot}25(\pm 0{\cdot}12)\pi - 6{\cdot}98 \quad (3)$$
$$n = 14 \quad r^2 = 0{\cdot}60 \quad s = 0{\cdot}40$$

As shown in Table 4, compound **20** has the highest pI_{50} value of all compounds considered in this study. We have previously discussed the motivation behind the synthesis of these class of compounds.[5] As can be seen from Table 4, our equation is capable of accurately predicting pI_{50} values of a series of 5-phenoxy analogs with the exception of compound **20**, which eqn (1) predicted to have a pI_{50} value of 6·4, whereas the observed value was found to be 9·0. The phenoxy-4-oxyacetate group is an outlier and should be considered separately.

3.2 Substituent effect at aromatic position 4 of aryltriazolinones

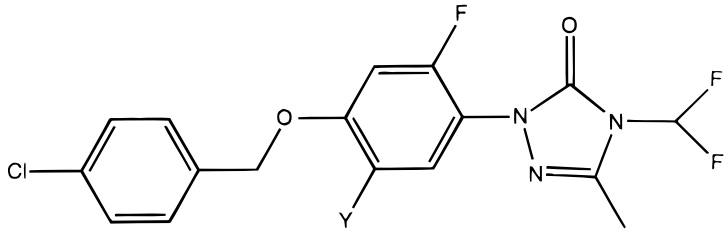
Several QSAR studies have been done on the aromatic 4 position of aryl tetrahydrophthalimide herbicides (Fig. 2).[10,11] These studies identified 4-chloro as the chemical group resulting in highest biological activity. In one of

TABLE 4
Biological Activities and Physical Properties of 4-Chloro-2-fluoro-5-(4-substituted phenoxy)phenyl Triazolinones



				pI_{50} ($-log\ M$)	
Compound	*Y*	π	*m.p.* (°C)	*Predicted*	*Observed*
15	OC_6H_5	2·08	oil	6·5	6·6
16	OC_6H_4-4-$NHSO_2C_2H_5$	1·52	151–152	6·9	6·6
17	OC_6H_4-4-OCH_3	2·18	oil	6·5	6·7
18	OC_6H_4-4-Cl	2·95	oil	5·8	6·7
19	OC_6H_4-4-NO_2	2·14	115–117	6·5	6·8
20	OC_6H_4-4-$OCH_2CO_2C_2H_5$	2·30	oil	6·4	9·0

TABLE 5
Biological Activities and Physical properties of 2-Fluoro-4-(4-chlorobenzyloxy)-phenyl Triazolinones



Compound	*m.p.* (°C)	*Y*	pI_{50} (*−log M*)	ED_{90} (*kg ha*$^{-1}$)
21	121–122	H	7·9	0·062
22	201–202	NO_2	NM[a]	>3·0
23	165–166	NH_2	4·9	>3·0
24	182–185	$NHSO_2CH_3$	4·9	>3·0
25	177–178	Cl	5·0	>3·0

[a] NM = not measured.

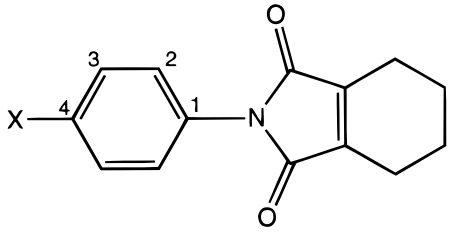


Fig. 2. 4-Substituted phenyl tetrahydrophthalimides.

these studies, a regression analysis of a series of 40 aryl tetrahydrophthalimide compounds, the electronic term σ and the Sterimol terms L, L^2 and B_5 explained 82% of the observed biological activity (eqn (4)).[10] The 4-benzyloxy group was also mentioned as providing good biological activity in the aryl tetrahydrophthalimide molecule, though this group did not fit eqn (4). There was no discussion of why both chemical groups provide good activity when they have widely different electronic and steric properties.

$$pI_{50} = 4{\cdot}062 - 0{\cdot}876\sigma + 2{\cdot}086L - 0{\cdot}370L^2 - 1{\cdot}079B_5 \quad (4)$$

$$n = 40 \quad r^2 = 0{\cdot}82 \quad s = 0{\cdot}345$$

In our previous QSAR work on 2,4,5-trisubstituted phenyl triazolinones[3] (Fig. 3), we had concluded that position 4 of the aromatic ring requires a hydrophobic

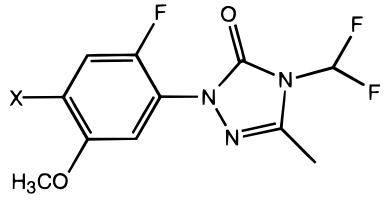
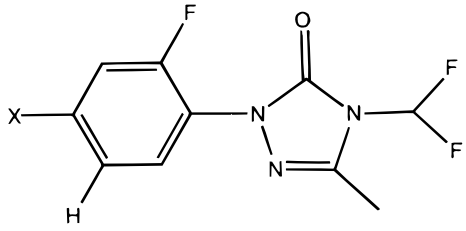


Fig. 3. 2-Fluoro-5-methoxy-4-substituted phenyl triazolinones.

TABLE 6
Biological Activities and Physical Properties of 2-Fluoro-4-substituted Phenyl Triazolinones



Compound	*X*	*m.p.* (°C)	pI_{50} (*−log M*)
21	$OCH_2C_6H_4$(4-Cl)	121–122	7·9
9	Cl	88–91	6·8
26	Br	81–84	6·1
27	F	69–70	5·3
28	NO_2	72–77	5·2
29	$OCH(CH_3)_2$	82–83	5·1
30	$NHSO_2CH_3$	172–174	<5·0
31	CH_3	59–62	<5·0
32	NH_2	oil	<5·0
33	OH	99–101	<5·0
34	H	oil	<5·0

and electronegative group such as chlorine for optimum activity (eqn (5)).

$$\log 1/ED_{90} = 0{\cdot}41(\pm 0{\cdot}09)\pi + 1{\cdot}27(\pm 0{\cdot}27)F_p - 0{\cdot}21 \quad (5)$$

$$n = 9 \quad r^2 = 0{\cdot}89 \quad s = 0{\cdot}21$$

A series of 2-fluoro-4-benzyloxy-5-substituted phenyl triazolinone derivatives was prepared in an attempt to understand the substitution requirements at the aro-

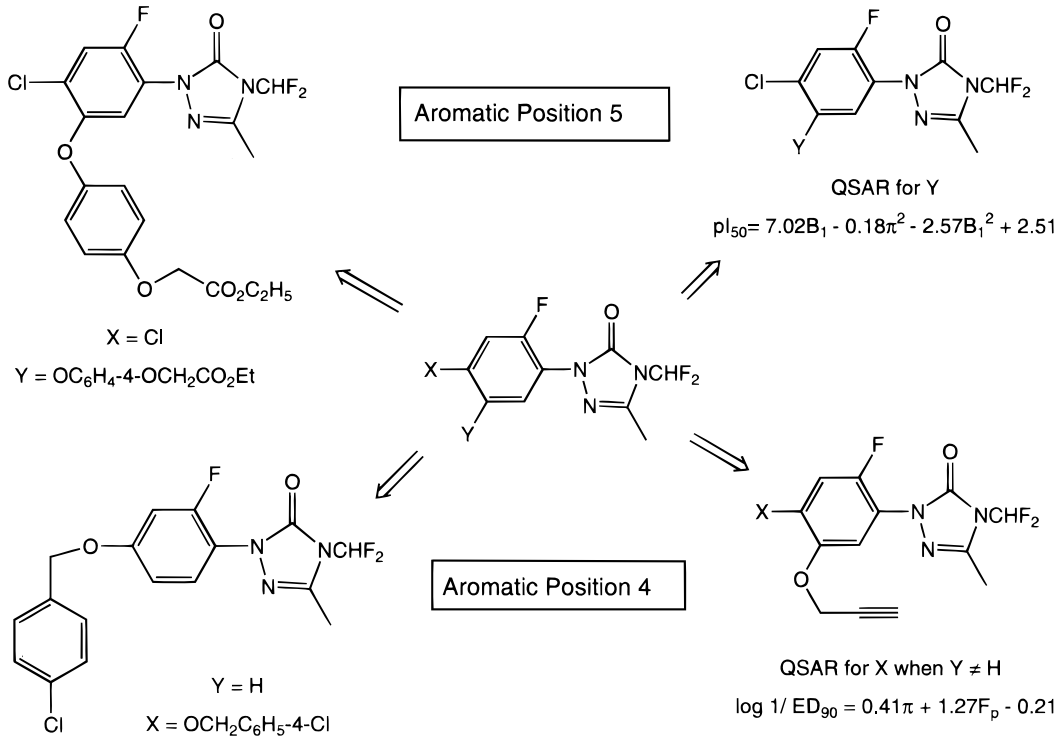


Fig. 4. Summary of QSAR and SAR for aromatic positions 4 and 5.

matic position 5 when a benzyloxy group occupies the aromatic position 4 of the aryltriazolinones (Table 5).

When we examined the biological activity obtained with this series it became quite evident that the 4-chlorobenzyloxy group in the 4 position of the phenyl ring results in good biological activity only when the group Y at the aromatic position 5 is hydrogen.

Next, a set of eleven 2-fluoro-4-substituted phenyl triazolinones was studied, but no significant correlation between biological activity and any physicochemical parameters was found (Table 6). The 4-chlorobenzyloxy group in compound **21** was found to give the highest biological activity, $PI_{50} = 7{\cdot}9$, followed by compound **9**, $pI_{50} = 6{\cdot}8$, with a chlorine in the 4 position of the aromatic ring.

4 CONCLUSIONS

The diversity of PPO-inhibiting chemical structures that have resulted in excellent herbicidal activity have in the past made it very difficult to determine the physicochemical parameters that are important for such activity. The use of the in-vitro cucumber assay resulted in the development of a regression equation for the aromatic position 5 of aryltriazolinones. Hydrophobicity and the minimum radius B_1 of groups at this position were found to be statistically significant in predicting the biological activity of the molecules. A parabolic relationship between π, B_1 and biological activity was found. Groups with large positive or negative π values decreased activity while minimum width, B_1, increased it. The latter effect may reflect steric interactions with a shallow receptor wall.

The in-vitro pI_{50} values correlated with the greenhouse pre-emergence biological activity only when the hydrophobicity term π was included in the equation. This explained the high pre-emergence greenhouse activity for compounds with negative π values in spite of their low intrinsic activity. A negative π value for a group at the 5 position of the aromatic ring will result in lower log*P* values and possibly better availability of the chemical to the plant through higher water/soil partitioning and root uptake. This explains to some extent why the $-NHSO_2CH_3$ group in compound **10**, with a relatively low pI_{50} value of 6·7 but with a negative π value of $-1{\cdot}18$, results in a highly active compound in the greenhouse when applied pre-emergence.

Though eqn (1) had excellent predictive power for all groups in the initial set, including the phenoxy group, it failed to account for the high activity of phenoxy-4-oxyacetate derivatives. We concluded that other factors, unaccounted for by eqn (1), were involved in the unexpected activity of these compounds. We have previously proposed that the higher-than-predicted biological activity of compound **20** could be a result of that compound closely mimicking the three-ring propionate portion of the tetrapyrrole substrate of the protoporphyrinogen oxidase enzyme.[5]

Analysis of structure–activity of aromatic position 4 also resulted in the development of two separate models, one for a 2,4,5-trisubstituted aryl triazolinone, with 4-chloro group providing optimum activity, and a

second model for a 2,4-disubstituted aryl triazolinone, with a 4-benzyloxy group providing optimum activity (Fig. 4).

The fact that we need to segregate the substituted phenyl triazolinone analogs into several different groups, based on their differing structure–activity properties, suggests that, though they are binding to the same active site, several binding modes within the same site could be possible.

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